Remarks

Claims 1-21 are pending. Claims 12-21 have been canceled. Claim 9 has been amended to remove the abbreviation for "*Helicobacter pylori*".

Election/Restriction

Applicants affirm the election of group I, claims 1-11, without traverse for prosecution.

Information Disclosure Statement

The Information Disclosure Statement filed on October 28, 2003 was resubmitted on January 29, 2004.

Specification

The Abstract has been amended to remove the abbreviation for oligodeoxynucleotides (ODNs) and cytosine-phosphate-guanine (CpG) dinucleotide motifs. The Summary of Invention has been amended to clarify the term, "CpG motifs".

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-11 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection.

The invention relates to the development of effective and long-lasting vaccines, especially vaccines incorporating nucleic acid encoding antigen, such as plasmid DNA, by encapsulating the DNA within a mucoadhesive controlled release particulate formulation. The specification teaches the use of these vaccine compositions to induce an immune response against pathogens such as malaria, anthrax, tularemia, and *H. pylori*. Applicants submit that

these examples are only meant to demonstrate the utility of the compositions and should not limit the scope of the claims. The standard for enablement is whether one skilled in the art would be able to make a vaccine as claimed.

For example, factors to be considered in determining whether a disclosure would require undue experimentation include, along with others, the state of the prior art and the predictability or lack thereof in the art. The prior art teaches the use of DNA in the production of vaccines against a vast array of diseases (see Watts and Kennedy Int. J. Parasitol. 29(8):1149-63 (1999)). See also the background of the invention at pages 4-6, which cite a number of DNA vaccines for bacterial, viral, and parasitic pathogens. See also the disclosure at pages 11-17. One could easily substitute these DNA sequences into the vaccine compositions described in the current invention to induce an immune response. Applicants are not claiming any unique DNA, merely DNA encoding antigens that are present in pathogens. Vaccines, including DNA vaccines, have been widely available for a long time. The invention here is to put them into a mucoadhesive controlled release particulate formulation. The application clearly provides support for such a formulation. See pages 17-28. Examples demonstrate the efficacy of these formulations.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 5, 6, 7 and 9 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claim 5 was rejected for an alleged lack of clarity in the term "less than 5 microns." The specification clearly defines the range of particulate diameters, and thus, the language is definite as used (see p. 26, lines 15-24). There is no requirement for a closed range in a dependent claim. The dependent claim is used to define the upper size range of the particles in the claim from which it depends.

Claim 6 was rejected because of the terms "approximately" and "ultrahigh." Applicants assert that one of ordinary skill in the art would be apprised of the meaning of "approximately 95% void volume" and "ultrahigh pressures" as they relate to controlled release polymer compositions (see for example US. Patent No. 5,456,917 to Wise et al.). There is an abundance of court decisions that have interpreted the meaning of "approximate", and the term is commonly used in issued U.S. patents.

Rejection Under 35 U.S.C. § 102

Claims 1-5 and 8-11 were rejected under 35 U.S.C. § 102(b) as being anticipated by O'Hagan Derek (Journal of Pharmacy and Pharmacology, Vol. 50, No. 1, pp. 1-10, 1997) ("O'Hagan"). Applicants respectfully traverse this rejection.

O'Hagan discloses the use of biodegradable microparticles as vaccine adjuvants. More specifically, this reference describes the encapsulation of antigens into poly(lactide-co-glycolide) microparticles. However, an important component of the claimed formulation is the requirement that the formulation be **mucoadhesive**, which enhances the effectiveness of the vaccine. O'Hagan does not teach or suggest that the poly(lactide-co-glycolide) microparticles adhere to

the mucosa nor do they teach an improvement of the microparticles to achieve mucoadhesion. Since this critical element is missing, this reference does not teach all of the claim limitations and therefore, does not anticipate the current claims. In this reference, the microparticles are an adjuvant, not a delivery system to enhance retention and delivery at a mucosal surface.

Rejection Under 35 U.S.C. § 103

Claims 1-11 were rejected under 35 U.S.C. § 103(a) as being obvious over O'Hagan et al., Molecular Medicine Today, (February 1997) ("O'Hagan"), in view of US Patent Application No. 2002/0197321 ("Seagar") and further in view of Flick-Smith et al., Infection and Immunity Vol. 70, No. 4, pp. 2022-2028 (2002) ("Flick-Smith"). Applicants respectfully traverse this rejection.

O'Hagan

As in the reference above, O'Hagan discloses the use of biodegradable microparticles as vaccine adjuvants. More specifically, this reference describes the encapsulation of antigens into poly(lactide-co-glycolide) microparticles. However, the reference does not teach or suggest encapsulating a nucleic acid in a **mucoadhesive** particulate formulation. Furthermore, O'Hagan does not teach anthrax or tularemia.

Flick-Smith

Flick-Smith discloses the encapsulation of recombinant protective antigen (rPA), the dominant antigen for protection against anthrax infection, in poly-L-lactide microspheres. In this reference, a recombinant *protein* is encapsulated, which is different from the current claims,

where a *nucleic acid* is encapsulated. Furthermore, Flick-Smith does not teach or suggest a mucoadhesive particulate formulation or the formation of an open-celled polymeric foam of approximately 95% void volume.

Seagar

Seagar discloses a vaccine composition in an orally administered solid dispersing form designed to disintegrate rapidly in the oral cavity. This reference teaches away from the present invention since the claims recite a **controlled release** particulate formulation. Furthermore, Seagar does not teach cryogenically grinding the matrix to an average particle size of 15 microns in diameter and sieving to isolate particles less than 5 microns in diameter.

The Combination of O'Hagan, Flick-Smith, and Seagar

For a *prima facie* showing of obviousness, the prior art references must teach all of the claim limitations. In addition, there must be some motivation to combine the references. O'Hagan, Flick-Smith, and Seagar fail to teach a vaccine composition containing an immunostimulatory nucleic acid encapsulated in a mucoadhesive controlled release particulate formulation. O'Hagan discloses mucosal administration of polymer formulations, but does not teach the improvement claimed by the present invention, which is the specific ability of the formulations to adhere to the mucosa.

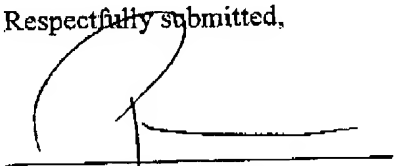
In addition, none of the references alone, or in combination, disclose all of the limitations of claims 6 and 7, which recite methods to form the vaccine composition. There is no teaching

with respect to the 95% void volume or cryogenically grinding the matrix to form particles of a certain size.

Finally, there is no motivation to combine O'Hagan and Flick-Smith, which teach controlled release, with Seagar, which teaches fast-dispersing dosage formulations. One of ordinary skill in the art would not look to the disclosure of Seagar to produce a vaccine composition encapsulated in a controlled release particulate formulation.

Allowance of claims 1-11, as amended, is respectfully solicited.

Respectfully submitted,



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AMENDMENT AND RESPONSE TO OFFICE ACTION

Certificate of Facsimile Transmission

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on the date shown below to the Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450.

Patrea L. Pabst

Date: March 22, 2004

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